DELAWARE STATE MEDICAL JOURNAL

Issued Monthly Under the Supervision of the Publication Committee
Owned and Published by the Medical Society of Delaware

VOLUME 19
NUMBER 7

JULY, 1947

Per Copy, 20c
Per Year, $2.00

CHRONIC SHIGELLOSIS DUE TO SHIGELLA SONNEI

A Case Report

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Shigellosis is an infectious disease, usually acute, caused by members of the genus Shigella. It is characterized clinically by the frequent passage of stools containing mucus, pus and blood, and accompanied by abdominal pain and tenesmus. Pathologically, there is an acute inflammation of the large bowel which leads to necrosis of the mucous membrane. The diagnosis is made by bacteriological examination of the feces.

Acute shigellosis is a rather commonly observed form of enteric disease, but the case with duration of illness of more than one month is not as frequent. The following case is presented because of several unusual features: (1) duration of illness of one year, (2) Loss of 2/3 of body weight, (3) a demonstrated bacteremia with possible endocarditis and (4) development of abdominal abscesses and empyema.

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Case Report

The patient, a 15-year-old Polish girl, while working as a maid in a seashore resort in the late Summer of 1944, became acutely ill with chills, fever and lower abdominal pain following a dietary indiscretion. She was removed to the local hospital with a diagnosis of acute appendicitis. On admission, physical examination revealed nothing remarkable, except abdominal tenderness in the lower left quadrant. Following consultation with members of the surgical and gynecological staff, surgical intervention was considered inadvisable, and a course of penicillin therapy instituted. During this treatment persistent fever and diarrhea occurred, and penicillin, along with a therapeutic trial of sulfonamides, resulted in little symptomatic improvement.

After a 12 weeks hospitalization, during

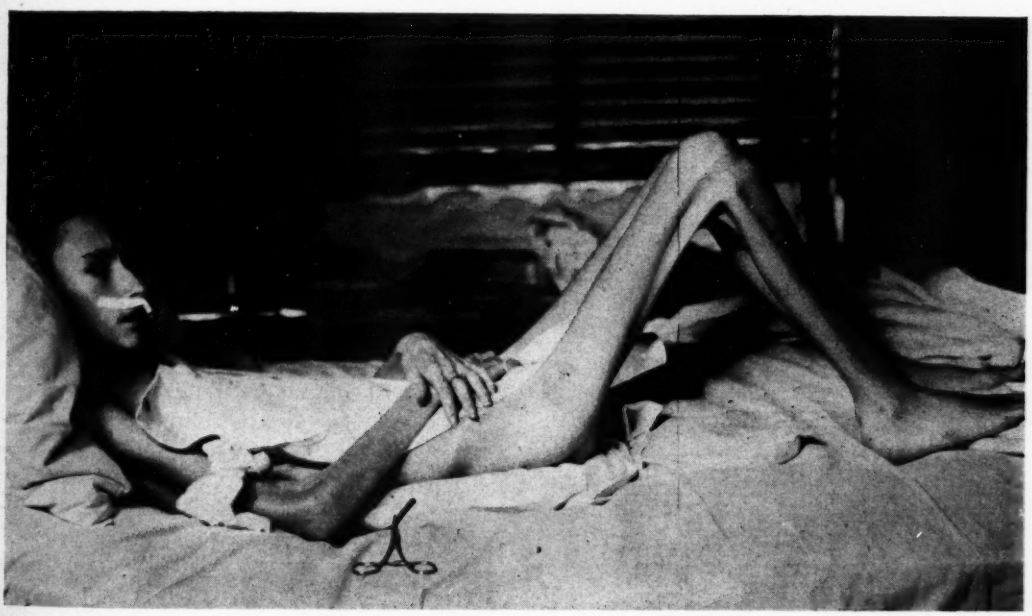

Fig. 1 Appearance of patient on admission January 1945 weighing 40 lbs. Normal weight 118 lbs.

which there was severe weight loss, continued unexplained fever and diarrhea, and after an additional 6 weeks under another physician's care, who prescribed rice diets, vitamins and tonics, with little symptomatic improvement, and continued weight loss, the patient was admitted to the Delaware Hospital on January 8, 1945. Physical examination revealed a critically ill, extremely emaciated child with a temperature of 100 F., a rapid pulse, a blood pressure of 100/40, enophthalmus, muddy sclerae, sunken cheeks, prominent facial bones, an eczematous area about the ears, prominent and easily counted ribs, hypoplastic breasts, and a scaphoid abdomen. The tongue and pharynx were red, teeth somewhat darkened, and gingivitis was apparent. No adenopathy observed. The scapulae were wing-like, the spinal processes prominent posteriorly, and the extremities were markedly emaciated with absence of subcutaneous fat. The muscles of the extremities were ribbon-like and tendon outlines were distinguishable. Bony structures of the elbows and knees were prominent. Body weight approximately 40 pounds. The lungs were clear, except some impairment at the left base. Breath sounds were prominent, no rales were heard. Silhouette of the heart was decreased. There was a loud, grade III, systolic murmer at the apex, which transmitted well into the axilla. The abdomen was tense with an area of rigidity in the lower left quadrant, no ascites present. At this time no etiological diagnosis was made. A chest x-ray showed the lungs clear, with atelectasis at the left base. There was a shift of the heart toward the left, and a flat plate of the abdomen was negative.

Laboratory Studies. An admission blood count disclosed a red cell count of 3.1 million, with a hemoglobin of 10 gm., 63%, and a white cell count of 24,000 with a marked left shift. Urinalysis was negative except for a 1 plus albumin and 5-10 white cells/hpf. Febrile agglutination tests were negative with typhoid, paratyphoid A & B, Br. abortus and Prot. OX19 antigens. The serum protein was 5.2 gm.%, and the stool showed a 4 plus benzidine test. Urine culture reveals the presence of coliform bacilli and stained urinary sediments showed no acid-fast organisms. After 24 hours incubation, a non-motile, aerobic gram-negative rod was isolated from an admission blood culture, and subsequently from a rectal culture. Typical non-lactose-fermenting colonies were observed on Difco SS agar, and triple sugar iron agar showed an acid butt with no gas, an acid slant, and no hydrogen sulfide production. This organism promptly fermented dextrose, maltose, mannitol, arabinose and rhamnose, with the production of acid; and no reaction on lactose, sucrose, xylose, dulcitol, sorbitol, inositol or salicin. Indol and acetyl-methyl carbinol were not produced, methyl red was positive and gelatin was not liquified. Slide agglutinations were negative with typhoid, polyvalent Flexner dysentery, Sh. ambigua and Sh. alkalescens anti-sera, and positive with Sh. sonnei antiserum. Tube agglutination with this antiserum agglutinated the organism through a titer of 1:320. After 8 days incubation it was noted that lactose and sucrose were fermented with the production of acid, and a tentative bacteriological diagnosis of *Shigella sonnei* was thereby submitted. This was later confirmed by Dr. Cora B. Gunther of the Enteric Disease Laboratory of the Penna. Dept. of Health, who reported similar biochemical and serological reactions. Thereafter an etiological diagnosis of shigellosis due to *Sh. sonnei* was made.

Hospital Course. The patient's subsequent course was quite eventful. She was stuporous, uncooperative, spoke in a weak voice and complained of pain. She would moan, refuse food and on one occasion the house resident reported he felt she was dying. Therapy consisted of tube feedings, glucose and saline by vein and three 500 cc. whole blood transfusions. Solu B was given intravenously, and multiple vitamin therapy, particularly B complex and C, was given by mouth. Sulfasuxidine sulfanilamide, neoprontosil and sulfadiazine were given therapeutic trials of 24 grams each, over a period of four weeks. No remarkable response was made to any of these medications. The blood and rectal cultures, however, taken on February 5th, were reported negative for *Sh. sonnei,* and remained negative on seven subsequent occasions. Under the above regimen, the patient began to show some symptomatic improvement, weighed 43 pounds, but continued to complain of pain in

the lower left quadrant. On February 26th, a sigmoidoscopic examination revealed no definite pathology, although the scope was passed only 15 cm. because of the acute angulation of the sigmoid and bowel wall. The entire wall was injected and bled when touched with cotton applicators and scope. Because of the continued persistence of pain and tenderness, a diagnosis of abdominal abscess was considered, and the patient was referred for surgery on May 1st. A lower left rectus incision was made, the abdomen opened, and immediately thereafter a large cavity filled with pus was broken into. This had apparently originated from the rectosigmoid junction. Two drains were inserted and the abdomen was closed. Culture of the pus showed coliform bacilli and alpha and beta hemolytic streptococci. Penicillin therapy, 500,000 units, was then administered. On May 11th, a definite dullness in the lower left chest was noted, and a diagnostic thoracentesis revealed about 50 cc. of muddy-colored, foul-smelling pus, which showed coliform bacilli and *Monilia krusei* on culture. No acid-fast bacilli were seen in direct smears. On May 14th, a left thoracotomy was performed and a double catheter inserted. Some improvement followed, but on May 16th, an x-ray showed a left pleural effusion, and an indirect communication to the thoracotomy pocket was demonstrated. On June 4th, a thoracostomy with rib resection was performed, and about a half ounce of thick pus was aspirated. By June 11th, this wound was clean and the packing was removed. However, a fistula subsequently developed from the fundus of the stomach to the draining empyematous space. By July 16th, there was little drainage through the thoracostomy tube, and the sinus to the stomach had apparently closed.

During this period the patient was maintained on a high calorie-high vitamin diet using forced feeding, and blood transfusions were given as indicated. In February she weighed 43 pounds, in March 52, and in April 60 pounds. During this latter period of complications she lost weight slightly, but continued to show slow improvement. She was finally discharged from the hospital on July 21, 1945, weighing 60 pounds, and referred to the out-patient department for follow-up. Weight gain was rapid thereafter, and when last seen on April 10, 1947, the patient was in good health and weighed 130 pounds.

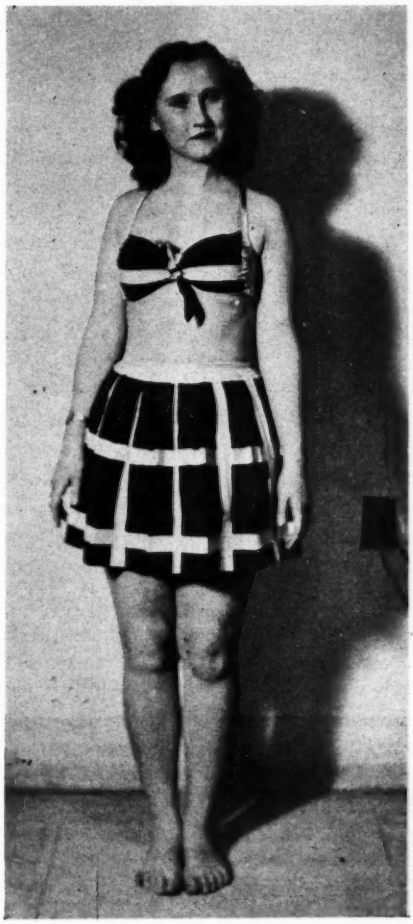

Fig. 2 Appearance of patient in Out-Patient Dept. April 1947. Weight 130 lbs.

CONCLUSION

A case of shigellosis of long duration has been presented. A bacteremia and possible endocarditis due to *Shigella sonnei* was demonstrated. Numerous complications including a pelvic abscess and empyema were reported. Although the patient lost and gained approximately two-thirds of her body weight over a twenty months illness, final recovery occurred.

CARDIAC DYSFUNCTION WITH SEVERE ANEMIA

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It is doubtful that anemia alone can cause structural heart disease (other than enlargement due to dilatation), yet in severe forms of chronic blood loss a picture superficially resembling valvular or coronary disease is often simulated. In 1918, Herrick stated that "blood of poor quality in arteries somewhat narrowed, can favor the development of anginal attacks." Later, both Pardee and Levine subscribed to this thesis: that severe anemia results in coronary insufficiency probaboly only in the presence of pre-existing coronary sclerosis. Accepting ischemia of the myocardium as the cause of anginal pain one would expect to encounter innumerable examples in everyday practice of patients with coronary disease exhibiting symptoms proportional to the presence of a varying secondary anemia. Such is not the case; indeed, an extensive review of cases of anemia made by Carter in 1943 revealed the coexistence of anemia and angina to be rare, actually less than one percent.

A review of the physiological factors tending to compensate for the decreased oxygen carrying capacity of the blood in any anemia is necessary for understanding the apparent lack of correlation. In dogs, Blalock and Harrison[1] showed that cardiac output and percent utilization of available oxygen in the blood are increased following hemorrhage.

Using the direct Fick method for cardiac output and determination of right auricular pressure by cardiac catheterization, Sharpey-Schafer[2] confirmed, in man, the work of Starling and Wiggers—that minute output is increased by raising the venous filling pressure in the right heart, by accelerating the heart, and by the action of adrenalin or related substances acting directly on the heart. Oxygen supply is then maintained by (a) increased cardiac output, (b) increased removal of oxygen in the periphery more or less proportional to the hemoglobin loss, and (c) reduced blood volume resulting in greater concentration of total hemoglobin. The latter effect is probably achieved through reduction in the vascular capacity of the capillary and venous systems, since clinical observation of the pulse, skin circulation, and calculation of total peripheral resistance indicate arterial dilatation. This is reflected in the increased pulse pressure, capillary pulsation in fingertips, and even "pistol shot" sounds over the larger arteries, a complex which has been termed the "hyperkinetic syndrome" by Harrison and has sometimes resulted in the erroneous diagnosis of valvular disease. A further compensatory factor is the high normal venous pressure, becoming definitely increased in the more severe cases. This rise in venous pressure does not seem to be simply the result of damming back of blood behind a failing heart but an integral part of the compensatory adjustment, mediated at least in part by reduction in peripheral vascular capacity.

Sickle cell anemia simulating coronary occlusion [3, 4] and heart studies in pernicious anemia[5] have been reported many times. Through autopsy study, the conclusion was reached that cardiac hypertrophy without valvular or endocardial abnormalities was secondary to the anemia, but that the exact cause was uncertain.

CASE REPORT

W. M., aged 50, entered the Delaware Hospital July 30, 1946, because of increasing shortness of breath, swelling of ankles, and weakness. The dyspnea occurred on slight exertion and required him to rest after walking as little as one block; substernal distress was never complained of. The past history was negative except for bleeding hemorrhoids of four years duration. Prior to admission he had been treated by a local physician for almost two years for heart disease, without a blood count having been taken.

Physical examination revealed an extremely pale but well nourished white male with no jaundice. The blood pressure was 106/50, with a pulse rate of 78/min. There were moist rales in the left lung base, with a blowing systolic murmur in the apical region. The liver and spleen were not palpable. One plus pit-

* From the Department of Cardiology, Delaware Hospital.
** Appreciation is expressed to Dr. Lemuel C. McGee for translations of the foreign literature and for helpful suggestions.

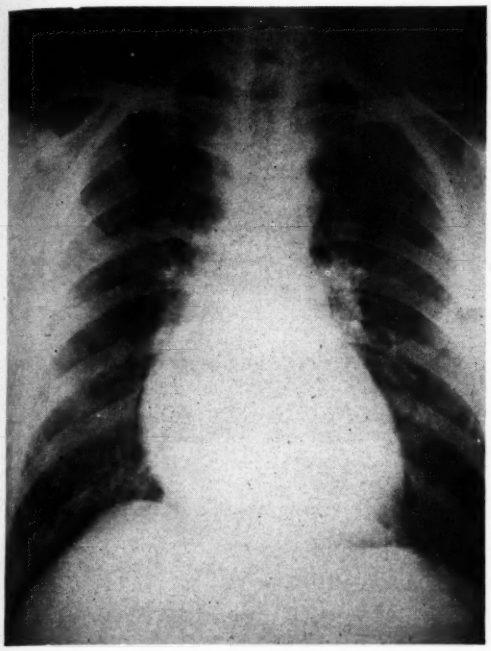

Fig. 1—Generalized enlargement of the heart. Cardiothoracic ratio 15.3 to 30. Pulmonary congestion.

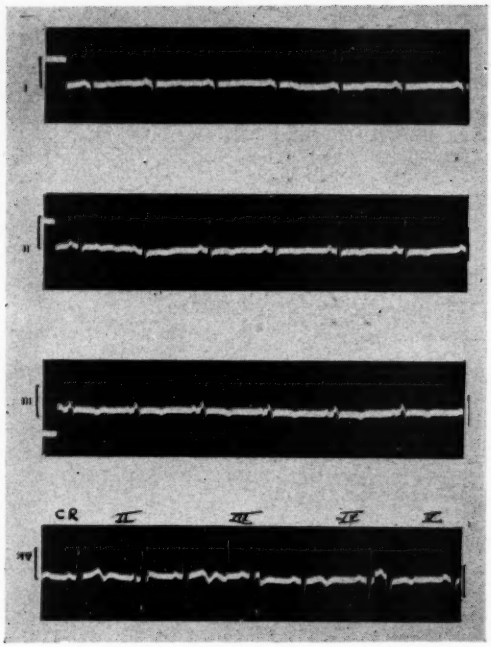

Fig. 2 St and T wave changes in limb and precordial leads of non-specific nature.

ting edema of the ankles was observed, and rectal inspection revealed large external hemorrhoids.

Laboratory findings were as follows: Hb 3.0 gms. (19%), RBC 2.4, color index, .4, severe hypochromia, WBC 5300 with a normal differential smear, reticulocytes 1.4%, and icterus index 2. Gastric analysis showed free hydrochloric acid, and the Wassermann Kahn tests were negative. Six foot chest plate (Fig. 1) showed generalized enlargement of the heart with a cardiothoracic ratio of 15.3 to 30. An electrocardiogram (Fig. 2) revealed T wave changes in all leads consisting of low amplitude in the limb leads, and inversion in the precordial leads over the left heart.

Following several large transfusions, a hemorrhoidectomy was performed by Dr. Daniel J. Preston, with uneventful recovery.

Just prior to surgery, at which time the Hb was 82%, and the RBC 4.3, a repeat chest plate (Fig. 3) revealed a normal heart size and a second ECG (Fig. 4) showed reversal to a normal pattern. Following operation, the systolic murmur, ankle edema, and basal rales disappeared. The patient has remained in good health and gave no evidence of anemia or cardiac abnormality eight months after discharge; he is now gainfully employed.

DISCUSSION

Despite the marked reduction in oxygen carrying capacity of the blood, no evidence of angina was ever present, and one would be inclined to conclude that no coronary disease existed. Certainly, it is difficult to base electrocardiographic changes on myocardial anoxia if one accepts the latter as the cause of anginal pain. Yet the T wave changes shown in Fig. 3 closely resemble the tracings taken on human subjects at simulated altitudes of 25,000 and 35,000 feet.[6]

In low pressure chamber experiments on young individuals EKG changes occur without any clinical evidence of the anginal syndrome. It would seem that the affects of cerebral anoxia will appear long before the syndrome of coronary insufficiency, except in those individuals who already have definite coronary disease of fairly marked degree. In the above case report vertigo and syncope based on cerebral anoxia were con-

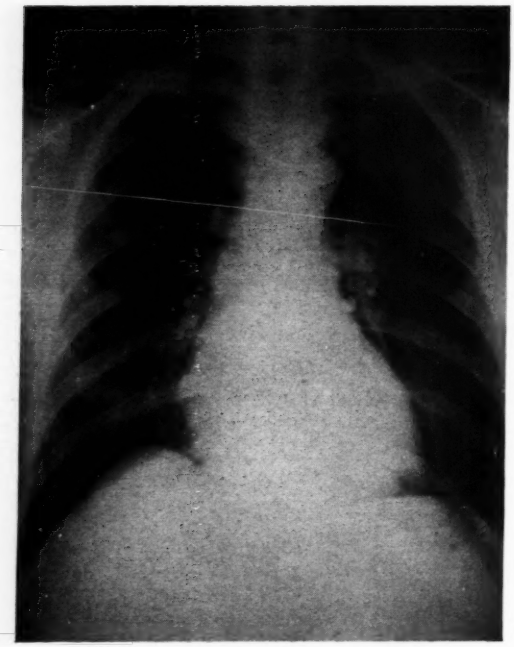

Fig. 3 Normal heart size following therapy.

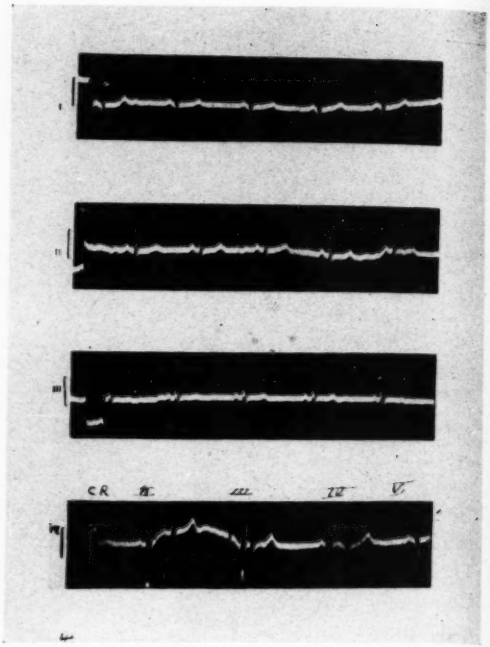

Fig. 4 Reversal of ECG to normal configuration.

spicuous, and the ECG changes are almost certainly attributable to reversible functional changes and/or to shifts in the electrical axis of the heart rather than to permanent myocardial damage. This alteration in sign, configuration, and potential are probably due to changes in chemical metabolism of the musculature. Even in known coronary disease the exercise test or the anoxemia test (which is approximately equivalent to breathing at an altitude of 18,000 feet) may give false negatives. It is interesting to note Amadeo's observation[7] that temporary anemia seems to benefit certain individuals with known coronary disease. He postulated that the anemia might stimulate the development of collateral circulation in the myocardium.

SUMMARY AND CONCLUSION

It appears that no definite correlation can exist between angina and anemia whether coronary disease is present or not. The compensatory factors operating in anemia: (1) increased cardiac output, (2) increased removal of oxygen in the periphery, (3) reduced blood volume, (4) the inability to ascertain any quantitative value for the degree of coronary sclerosis present (short of autopsy), (5) the necessary curtailment of physical activity in the presence of moderately severe anemia and (6) perhaps the greater vulnerability of the cerebrum to the affects of anoxia, militate against any such correlation.

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CLINICAL PATHOLOGICAL CONFERENCE

Delaware Hospital Case #29

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Four months prior to admission the patient, a 17-year-old male, who had been in good health all his life went to a C. C. C. camp. One of his barracks mates had a bad cough and one month later the patient developed a chronic cough, productive of whitish sputum with occasional flecks of blood in it. He began to lose weight, and become short of breath. Towards evening he would get chilly and sweat profusely, he also noticed that he was getting hoarse. He entered the Delaware Hospital on November 9, 1937, four months after onset of illness, his weight having dropped from 148 to 117 pounds. Physical examination revealed a thin, pale, anemic and weak looking white male about 17 years old. There was moderate enlargement of the posterior cervical glands. The thyroid was not palpable. Heart and lungs were negative. The axillary, epitrochlear, inguinal and posterior cervical glands were enlarged, especially the cervical. There was a light red maccular rash over back. On admission the urinalysis showed a neutral reaction. Specific Gravity 1:029; a faint trace of albumin, loaded with amorphous phosphates and bacteria. The blood count demonstrated a hemoglobin of 63%, RBC 3,900,000; WBC 40,500; Polys 2%; lymphocytes 97%; myelocytes 1%. Heterophile antibody reaction was negative except for slight agglutination of paratyphoid and typhoid antigens to dilutions of 1:20 and 1:80 respectively. Wassermann and Kahn tests were negative. The Sedimentation Rate was 33 mm. per hour and the blood culture was negative. An x-ray of the chest showed a large amount of mottling in the region of the hilus on the right side extending towards the apex and base, also enlargement of the mediastinal glands which gives indication of an early pulmonary tuberculosis. A flat plate of the abdomen showed the liver shadow extending to the iliac crest. A gastro-intestinal series was negative.

During the hospital course of 56 days, terminated by death, the patient ran a daily spiking intermittent fever from a normal A. M. temperature to 103 and 104 degrees in the evening. A lymph node biopsy was performed, on November 12, 1937, which showed microscopically hyperplastic proliferating lymph follicles without any destruction of normal architecture, diagnosed as non-specific lymphadenopathy. He became progressively weaker and continually complained of pain in L. U. Q., sore gums, and difficulty in getting his breath. The red count and hemoglobin slowly dwindled despite one transfusion. One month after admission his RBC was 2,800,000, Hemoglobin 46% and at time of death his RBC 1,700,000, Hemoglobin 40%. The white count varied from 9,800 to a terminal flare up to 91,000. The differential remained essentially the same with the lymphocytes always above 90% and with 1-2 metamyelocytes. Two platelet counts were 50,000 and 60,000 done one month apart. His Sedimentation rate remained above 30. Tuberculin tests were negative. A repeat Widal one month after admission was positive at 1:40 dilution. Blood culture 3 days prior to death was positive for hemolytic staphylococcus. Four days prior to death he became quite dyspneic, this increased markedly during the next two days, his neck glands were enlarged. A pseudomembrane formed in his throat, and there was a great deal of mucoid exudate, he was barely able to get air through the obstructed respiratory passage. A tracheotomy was done. The patient died during the operation. During his hospital course he was given 2 cc. of liver extract daily along with other drugs for comfort of the patient. An autopsy was performed.

DIFFERENTIAL DIAGNOSIS: E. A. MEKANIK, M. D.,*

We have here the case of a 17-year-old male, who, according to the history had been perfectly well up to three months prior to admission. At that time he entered a camp where he was exposed to a barracks mate with a "bad cough." If we were to read only the history of the present illness, either tuberculosis or typhoid is a possibility. The patient developed a cough, blood tinged sputum, loss of

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weight, some dyspnea, and apparently elevation of his afternoon temperature, which suggested tuberculous infection. Since until about three months prior to admission, this boy was apparently well, this disease is one with a fairly rapid course. The physical examination is significant in that it presents a picture of a rather acutely ill patient. Notable, is the presence of the enlarged cervical glands with a co-existing generalized lymphadenopathy and an enlarged liver. This appears to be one of the most prominent features of the case. Lymphadenopathy is usually divided into four groups, (1) Inflammatory; (2) chronic granulomas (tuberculosis, lues); (3) malignant lymphomas and lymphoblastomas; and (4) secondary tumors. Inflammatory lesions of lymph nodes are usually due to virulent bacteria being arrested in the lymph nodes. The glands are usually enlarged, painful and tender. Suppuration occurs but rarely. Tuberculosis and syphilis are the two greatest offenders in the chronic granuloma group. Syphilis may cause node enlargement in any stage, but generalized adenopathy is only characteristic of secondary lues. With the negative Wassermann, it seems reasonable to rule out syphilis. Tuberculosis one of the commonest causes of lymph node enlargement. Usually these are local, but generalized adenitis is not unknown, especially with a virulent, diffuse infection. Considering lymphoblastomas, there is Hodgkins disease, which also presents a similar picture. Though a generalized adenitis is a common manifestation, cervical gland enlargement is usually detected first. Certain features of this case can be easily covered by Hodgkin's disease. Lymphosarcoma, leukemia and possibly thymomas are others grouped as malignant lymphomas, and likewise are capable of presenting a similar picture. Secondary tumors complete the classification; the patient's age, the comparatively short course, and the non-committal pathological report, I believe, rule it out. We see by our laboratory studies that, first, there is apparenlty no primary kidney disease. However, the fact that bacteria are present in the urine is significant in view of the fact that typhoid is one of our possibilities. Urine cultures certainly were indicated, and were probably done since the patient was hospitalized for fifty-six days. The white count of 40,000 with 97% lymphocytes certainly is an outstanding feature. Here, with a count of 40,000, of which 97% are lymphocytes, one immediately thinks of a primary disease of the lymphatic system and lymphatic leukemia fits the picture best. The anemia could be explained on the basis of either involvement of the hematopietic system or as due to a chronic illness with deficient nutrition. The heterophile reaction may be significant. A titre of 1:80 for typhoid antigens is considered by some as diagnostic of typhoid infection, but others say that more than 1:80 is required to be significant. At any rate, it only seems to cloud the issue; with more information, its significance would either increase or decrease. We have therefore the following possibilities: Tuberculosis, typhoid, inflammation unspecified of lymphatic system, chronic granuloma (tuberculous), Hodgkin's disease, lymphosarcoma, leukemia, etc., or secondary tumors.

Tuberculosis, especially the miliary variety, is certainly a possibility. For it we have a history of suspicious contact, loss of weight, cough, blood tinged sputum, sweating and chills, and an afternoon temperature elevation. In addition, there is x-ray evidence of an early pulmonary lesion. To offset all this evidence we have a *negative* tuberculin test, which, to my mind, means there has been no previous tuberculous infection. If I am wrong, then possibly the picture is clear, and the response is a terrific outpouring of the lymphatic system, but certainly the biopsy report would have mentioned findings typical of tuberculosis.

Typhoid. Because of the possible exposure at the camp, and the Widal titre of 1:80, typhoid should be mentioned. However, against this diagnosis is the repeat titre of 1:40 one month later, which certainly should have been higher. The tender abdomen may have been due to diffuse involvement of the lymphatics of the intestine, but generalized clinical adenopathy is uncommon in typhoid. We would also expect splenomegaly instead of the gross hepatomegaly mentioned. No mention was made of the pulse, which is slow and full in

typhoid. The remittant fever is also against this diagnosis. Bacteria were mentioned as being in the urine, and culture would have helped in many ways. A rash is mentioned in our history, but the typhoid rash is unusual after six weeks. Finally, we have a high leucocytosis and absolute lymphocytosis, which is definitely uncommon in typhoid, and the mode of death is not in keeping with typhoid patients. Of more significance to me is the possibility of a primary disease of the lymphatic system. The inflammations do not seem a logical choice; first, we would necessarily have to have a primary focus for a diffusion point, and none is apparent. Then, too, there is invariably a polymorphonuclear reaction to such invasion, and here our reaction is an absolute lymphocytosis. Finally, the entire lymphatic and reticulo-endothelial system is not involved, as we have here.

The most likely choice is lymphoblastoma, malignant lymphoma, i. e., Hodgkin's disease, lymphosarcoma, and leukemia. Of these, lymphosarcoma seemed to be the most likely, principally because of the biopsy report. In the late stages tumor invades the surrounding tissues, but early the gland is intact, with replacement of normal lymphoid structure. Anemia, which is present in our case, may be a prominent feature of lymphosarcoma. Fever, progressive diffuse lymphadenopathy, and a relative and absolute lymphocytosis are common. Terminally these cases go out with a picture of lymphatic leukemia; they often bleed rectally, due to involvement of the intestinal mucosa. Sore gums are common as are rashes similar to that of the patient under consideration. The only disconcerting feature is the lack of mention in the report of the spleen. An x-ray of the abdomen mentions only hepatic enlargement, but it does say the patient complains of left upper quadrant pain which may have been due to a progressive splenomegaly. These patients fail progressively, as our patient did, and it is not uncommon for them to develop obstruction of the trachea, when the lymphadenopathy centers in the mediastinal and cervical glands. Our report emphasized that the cervical chain was very markedly enlarged. This is also characteristic of Hodgkin's disease, which, also tends to involve the mediastinal glands through this is also shared by lymphosarcomas. The principal features against Hodgkin's disease are the blood count and the biopsy findings. The possibility of a leukemia is obvious, and its symptoms, signs and laboratory data are fairly well known by all of us.

DR. MEKANIK'S DIAGNOSIS

Lymphosarcoma or one of the lymphomas.

AUTOPSY DIAGNOSIS

Malignant thymoma with leukemia (leukosarcoma) with extension to pericardium, pleura, lymph nodes, spleen, liver, and bone marrow.

PATHOLOGICAL DISCUSSION

DR. JOHN W. HOWARD*: The autopsy reports the upper mediastinum firmly adherent to the sternum and made up of a densely fibrous structure which encircled the superior vena cava and branches of the aortic arch and caused compression of the trachea. Gross section of this mass revealed soft tumorous glands and thymus. The involved pleura measured up to 5 mm. in thickness. The pericardial sac was obliterated. The liver weighed 2100 gms. and was firm throughout. Microscopic section of the mass revealed a tumor not unlike lymphosarcoma consisting of uniform infiltrating cells either lymphoblasts or altered thymic cells. Figure 1 is from this area and shows a persistent Hassall corpuscle. Other organs including the liver showed infiltration with similar tumor cells. The bone marrow (Fig. 2) showed complete replacement with identical cells. The tumor is a lymphosarcoma involving the thymus together with a frank lymphogenous leukemia. The process may well have started in the thymus. It is also quite likely that the leukemia and sarcoma are all part of one disease. The inter-relation of the various lymphomas and leukemia has gradually appeared in the literature and Mallory[1] suggested in 1914 that Hodgkin's disease, lymphatic leukemia, lymphosarcoma, and various sub-varieties were inter-related. Other writers have been gradually inclining toward this opinion. Recently Herbert[2] reported on the relation of Hodgkin's disease, lymphosarcoma and reticulum sarcoma. R. P. Custer[3] recently reported the frequent association of leukemia with a number of lymphomas which appeared

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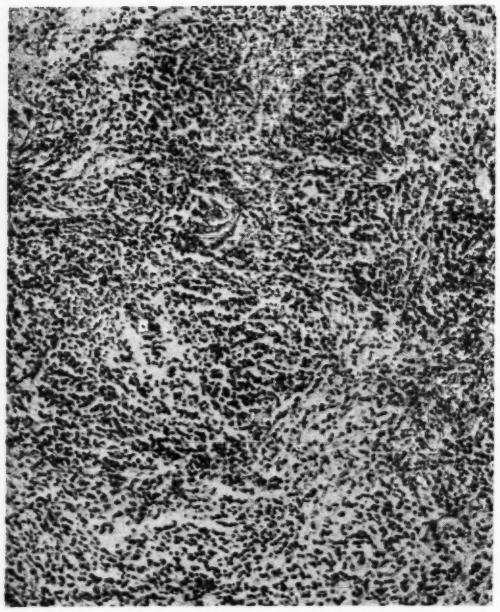

Fig. 1 Tumor of thymus with Hassall's Corpuscle. x137.

histologically different in separate areas or periods of biopsy. Forkner[4] presents an excellent review on the subject of leukosarcoma and indicates this disease is more common in the younger age and frequently involves the mediastinum. Cook[5] found that lymphosarcoma often associated with a leukemia blood picture, is the common form of massive mediastinal enlargement in children. The nine cases she added to a collected series of 74 represented 24% of 38 cases of acute leukemia seen during a period of six years. Several reported cases have done well on x-ray but one must always remember that large doses may produce added enlargement of the mediastinum and further respiratory obstruction. Pathologically any large tumor of the anterior mediastinum that surrounds great vessels should be suspected of having arisen in the thymus. Definite histological proof of involved thymus is not easy and rests entirely on the identification of Hassall's corpuscle.

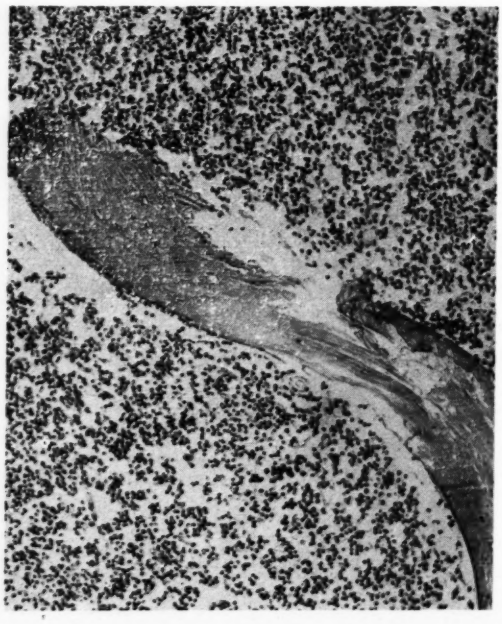

Fig. 2 Bone Marrow. x137.

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EXPERIMENTAL TRANSPLANTATION OF OVARIAN TISSUE INTO THE TESTIS CAPSULE FOLLOWING ORCHIC PARENCHYMECTOMY

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While there is practically no experimental evidence to justify the following procedure, the exigency of the following cases would seem to entertain almost any gesture of reparation.

CASE I

A white man, 71 years of age, had a radical prostatectomy for carcinoma September, 1945. As his general condition was satisfactory and there was no clinical or laboratory evidence of metastases, orchectomy was held in reserve until such time as it would be indicated. He returned to work and was comfortable until April, 1947, when he complained of weakness, which he attributed to his caring for a sick wife and son at home when his day's work was done. He had been taking hexestrol 3 mgm. daily for the intervening time since his operation. The blood picture at this time was as follows: Hb, 78%; red cells, 3,700,000. It

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was felt that he was probably developing a metastasis and x-ray verified this suspicion, showing lesions in the ilii and femora.

He was admitted to the hospital and bilateral orchic parenchymectomy carried out in the following manner. When testis capsule was incised in the long axis of its convex border the seminiferous tubules were removed by tissue forceps (gauze being avoided). No bleeding vessels in the capsules were ligated. An ovary that had been removed an hour previously and kept in plasma was now bisected and one-half dropped first into one testis capsule and then the other half into the other testis capsule. Each capsule was closed with a running suture of 0000 chromic catgut. The scrotal skin was closed without drainage with black silk. Primary healing took place in 6 days and, aside from transient local tenderness for several days, at the end of one month the scrotal contents were firm and not tender, and the scrotum presented a normal appearance.

25 days following operation the patient returned to work.

40 days following operation the blood picaure was as follows: 93% Hb., red cells, 4,900,000. Acid phosphatase, 0.5 Bodansky (modified).

X-ray of the lungs—negative.

CASE II

A Negro, aged 63, was referred for the alleviation of obstructive symptoms referrable to the neck of the urinary bladder. On rectal examination the family doctor found a stony, hard prostate. Our examination agreed with this, the impression being that of a "frozen pelvis." As acute retention of urine had not occurred we decided to do orchic parenchymectomy which might oviate subsequent electric reversion of the vesical neck, through local regression of the malignant prostate.

Prior to operation the blood count was as follows: Hb., 80%. Normal differential count. Patient in fair stage of nutrition. No metastases demonstrable in chest or bones.

On May 15, 1947, bilateral orchic parenchymectomy with ovarian transplantation was carried out according to the technique described in Case I. Healing of the scrotal wounds was rapid and complete in eight days. As in the first case there was local tenderness for the first week. Both cases received 100,000 units penicillin q. 4 h. (i. m.) for one week following operation, which probably contributed to the primary healing of the scrotal wounds. There was noticeable improvement in the local vesical neck sypmtoms and the patient was discharged from the hospital 12 days following operation, the scrotal wounds completely healed.

COMMENT

Autotransplantation has been successful in mammals from one individual to a second site in the same individual or from one individual to a closely related individual. Grafts of ovaries of one species into another (heterotransplantation) or even of unrelated animals of the same species are but questionably or never successful.

Ovaries transplanted into adult intact or castrated male rats fail to show cyclic changes of the usual type. The ovarian follicles grow but fail to ovulate and corpora lutea do not form. It is known that male rats hypophyses contain more gonadotropin than those of the females but that they will not establish rhythmic relationship with the transplanted ovaries, while ovaries transplanted into ovariectomized adult female rats show the usual cyclic changes.

We were led to try this experiment after reading of Whitney's experimental work in female dogs of different breed. (Science, 103: 654, May 24, 1946). He reports successful transplantation of ovaries when the transfer was made while both animals (donor and recipient) were in estrus. In the successful transfers the donors were blood hounds and the recipients foxhounds. (After incisions of the capsule the ovary was removed at the hilus and transferred to the capsule of the recipient which was then closed with fine catgut sutures). It may well be that here is a biological factor that may have great significance: the site of implantation. After transfer, signs of estrus in the recipient decreased gradually over a period of four or five days. Estrus then recurred in full intensity and continued for a normal period of twenty days. Signs of a sec-

ond estrus were observed forty-nine days after the start of the previous period in one foxhound and on the ninety-eighth day in another. These periods did not correspond with the recipients' previous history but represent a continuation of the donors' cycle. One of the dogs was sacrificed seventy days after termination of the second estrus. On microscopic study the ovaries appeared normal except for a few necrotic vessels at the hilus; otherwise vascularization was well advanced. Although the granulosal cells were first thought to secrete the primary ovarian hormone, recent histological and histochemical studies indicate that the theca interna is its source.

Whether or not the transplanted ovarian tissue will continue to function in its new environment in the above two cases remains to be seen.

CLINICAL USE OF STREPTOMYCIN*

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Although streptomycin is an effective drug in the treatment of certain bacterial infections, its use necessitates careful supervision if optimal results are to be obtained. In the time allotted for this discussion we will consider the more important factors regarding the successful use of this new antibiotic agent.

IDENTIFICATION AND SENSITIVITY OF INVADING ORGANISM

Streptomycin should be used only where there is an infection due to a streptomycin-sensitive organism. Although clinical results with streptomycin do not invariably parallel antibacterial potency, as determined in vitro, it is important to identify the causative organism and measure its sensitivity to the drug in order to determine its potential effectiveness in a given infection. Not infrequently, ordinarily susceptible organisms develop a resistance to streptomycin, especially when inadequate dosages of the drug are employed, or in those cases where it is necessary to readminister streptomycin. Hence, it is very important, not only to determine the nature of the infection for the prognosis, but also for the adjustment of the dose of streptomycin.

As yet the complete range of antibacterial activity of streptomycin has not been determined. In vitro studies have indicated that streptomycin possesses high activity against a number of organisms, notably Escherichia Coli, Mycobacterium Tuberculosis, Bacillus Mycoides, Eberthella Typhosa, Pseudomonas Aeroginosa, Proteus Vulgaris, Salmonella Schottmullerii, Hemophilus Influenzae, Bacillus Mucosa Capsulatum, Bacterium Tularense, Hemophilus Pertussis, and the Brucella Abortus organisms. Furthermore, many ordinarily penicillin-susceptible organisms which have become penicillin-fast are controlled by streptomycin.

Thus far, the clinical use of streptomycin has been modified by supply and cost. Because of this it has been employed largely in those infections, the course of which penicillin and the sulfonamides have been unable to effect. Most prominent of these are gram-negative infections of the urinary tract, pulmonary and meningeal infections due to Friedlander's bacillus and Hemophilus Influenzae, bacteremias due to gram-negative bacilli, such as E. Coli, H. Aerogenes, B. Proteus, and Salmonella and wound infections. Excellent results have been obtained in Tularemia, particularly the ulceroglandular type. Clinical observations dealing with the treatment of Brucellosis are promising, especially in acute cases, but not conclusive. Furthermore, there is suggestive evidence that streptomycin may prove beneficial in the control of pertussis.

According to preliminary reports from the Mayo Clinic, streptomycin probably exerts a limited suppressive effect on some of the more universal types of pulmonary and extra-pulmonary tuberculosis. Already streptomycin has been used successfully as a prophylactic agent in preparing cases for large bowel surgery. In addition to the above, there have been many miscellaneous infections treated with streptomycin with varying success. However, further clinical studies must be completed before an evaluation can be made regarding this new substance.

ADEQUATE CONCENTRATION OF STREPTOMYCIN AT SITE OF INFECTION

Streptomycin must be administered in such

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* Read before the Delaware State Medical Society, Dover, October 8, 1946.

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a way that it comes in contact with the infecting organism in effective concentrations. Studies on the absorption and excretion of streptomycin in man have shown that this antibiotic, administered parenterally, behaves like penicillin, in that both agents are rapidly absorbed and rapidly excreted in the urine. Therapeutic blood levels are easily obtained by intermittent intramuscular injection or continuous intramuscular drip. It has also been given orally, intrathecally, and by nebulization into the tracheobronchial tree. When administered parenterally, streptomycin has been detected in pleural, anmiotic, intraocular, and ascitic fluids in concentrations approximating that level in the circulating blood. In humans without disease of the cerebrospinal apparatus, streptomycin does not readily diffuse into the cerebrospinal fluid; however, in the presence of bacterial meningitis, appreciable amounts reach the cerebrospinal fluid. Furthermore, after systemic administration, little if any of the drug is found in the feces. Also, when streptomycin is ingested, little of it diffuses into the blood stream, and, therefore, none appears in the urine. However, streptomycin is not destroyed in the gut and is, therefore, a suitable agent for the control of certain infections involving the intestinal tract.

Thus far, the dosage of streptomycin has been influenced somewhat by the limited supply. As supplies increase, larger doses of the drug will probably be used. Obviously such factors as susceptibility of causative organisms and the type, severity, and location of the infection tend to influence the dosage requirements in each case. In general, the daily dosage usually employed has been 3 to 4 gm. equally divided in 6 to 8 doses for 5 to 10 days. The best results being obtained when large doses are given over a relatively short period of time. In other words, it is advisable to attempt a "knock-out" of the infection, rather than run the risk of the infecting agent's becoming streptomycin-resistant as a result of prolonged therapy with small amounts of drug. For most infections requiring streptomycin, it seems that intermittent intramuscular injections of the drug give the most satisfactory results. For intramuscular use, streptomycin (1 gm.) is dissolved in 10 cc. of sterile distilled water or sterile physiologic saline. In order to avoid pain, it is advisable that the injection be made slowly, and if desirable procaine hydrochloride (1.0% solution) may be used. For infants the daily dose is approximately 5 mg. per pound of body weight.

As indicated, streptomycin may be administered orally. This method is reserved for those conditions limited to the gut, such as certain salmonella infections or in preparation of patients for bowel surgery. Oral administration is also indicated in infections, such as typhoid fever, when parenteral administration is also employed. As a rule, smaller daily dosage, 0.5 gm. to 2 gm., in 4 divided doses will suffice when the drug is used orally. Fruit juice and milk are suitable vehicles for the streptomycin. In the treatment of certain types of meningitis, it seems advisable to supplement systemic therapy with the intrathecal administration of streptomycin. For this purpose, 25 to 30 mgm. in 5 cc. of physiologic saline solution is given by the subarachnoid route. For the control of infections involving the larynx and tracheobronchial tree, streptomycin is used satisfactorily by means of nebulization. For nebulization between 0.5 and 1 gm. are used daily. The drug being dissolved in approximately 6 to 10 cc. of physiologic saline solution and inhaled from the nebulizer six times a day.

SUPPRESSION OF INFECTING ORGANISM

In every instance it is important that streptomycin be continued in adequate amounts until the infection is suppressed. Obviously, it is difficult to state the point at which streptomycin should be stopped in a given infection. In many instances it is not easy to determine when the infection has disappeared. Furthermore, one cannot measure the immunity response of the patient and, if sufficient immunity has not developed, the possibility of a relapse exists. Thus, one cannot outline a course of therapy with streptomycin which will theoretically be effective in all cases. However, it seems practical to overdose the patient for a short period of time, 5 to 10 days, than to overdose him and run a greater risk of inducing a drug-resistant organism as well as the danger of developing a neurotoxic reaction to the drug. Of course, in

the treatment of a disease, such as subacute bacterial endocarditis, past experience has indicated that it is important to prolong the treatment for at least 50 days, in order to prevent relapses.

ERADICATION OF FOCI OF INFECTION

At some point in all infections there is a portal of entry. In many instances the portal is obvious but in others it is obscured. For the treatment of septicemia with streptomycin, the most important single factor is the location and removal, or drainage, of the focus of infection by proper surgical procedures to prevent reinfection of the blood stream. Also, many urinary tract infections are produced as a result of infection in other structures, such as the skin, bones, intestines, and the genital tract. Although necrotic tissue or pus in a lesion does not greatly influence the action of streptomycin, the presence of a collection of pus demands prompt surgical drainage. The evacuation of pus thus permits streptomycin to deal more effectively with the infected tissue.

Not infrequently, an underlying causative organic lesion, such as an obstructive uropathy in urinary tract infections, will give rise to disappointing end results with streptomycin. The presence of such lesions per se is not a contraindication for streptomycin, but it does constitute an important factor as regards permanent cure with the drug. It is imperative that all preexisting organic abnormalities be corrected while streptomycin is being administered. When one considers the rapidity with which streptomycin-resistant organisms develop, the importance of this is obvious.

RECOGNITION AND CONTROL OF STREPTOMYCIN TOXICITY

Streptomycin resembles penicillin in that it has a limited but definite toxicity for man. Fortunately, most of the untoward reactions appear to be transient and not of a serious nature, although in some instances it is necessary to discontinue the use of the drug. Furthermore, sensitization to streptomycin is observed in certain cases receiving interrupted therapy. Hence, all patients who are treated with the drug should be watched carefully for various reactions.

The most serious reaction to streptomycin is a disturbance of the eighth cranial nerve, as manifested by dizziness, tinnitis, vertigo and deafness. This reaction occurs usually after relatively large doses of the drug have been administered over long periods. Approximately 10 per cent of patients receiving streptomycin for more than 14 days will develop manifestations of this neurotoxic effect. In the patients so affected, there seems to be no objective evidence of improved labyrinthine function, although there does occur some functional compensation for the disability. When large doses of streptomycin are being used for longer than two weeks, the patient must be followed closely for the occurrence of diminished auditory acuity, tinnitus, or vertigo. If any of these should develop, then the drug is best discontinued, unless streptomycin is the only available life-saving measure.

In contrast to the above, the following untoward reactions have been produced by streptomycin: Arthralgias, myalgias, headaches, nausea and vomiting. Fever and skin rashes likewise have been noted. Seldom do these toxic effects require the withdrawal of streptomycin.

AVOID THE USE OF STREPTOMYCIN FOR MINOR INFECTIONS

As indicated, streptomycin is an effective agent against a variety of gram-negative and gram-positive bacteria. However, it does possess definite disadvantages, namely, streptomycin-sensitive organisms will develop resistance to the drug quite rapidly, and sensitization to streptomycin has been noted in individuals in which interrupted treatment was employed. Therefore, it seems reasonable that streptomycin be employed only in the treatment of serious infections where there is no other effective form of therapy. Certainly streptomycin should not be used in the control of medical trivialities.

SUMMARY

In streptomycin we have another remarkable antibiotic agent for the control of many types of bacterial infections. However, its rational use in the treatment of disease requires an understanding of certain factors inherent in this type of therapy, namely:

1 Identification and sensitivity of invading organism.

2. Adequate concentration of streptomycin at site of infection.
3. Suppression of infecting organism.
4. Eradication of foci of infection.
5. Recognition and control of streptomycin toxicity.
6. Avoid the use of streptomycin for minor infections.

DISCUSSION

DR. JOHN W. LYNCH (Seaford): Mr. President and members, as I sat and listened to Dr. Flippin's masterly presentation I certainly felt that it didn't behoove me to get up here and say anything about streptomycin. I have personal knowledge of only one case, and other than that what I do know about it is what I have read. I feel sure also that not many general practitioners have had an opportunity to use streptomycin, but now that it will be more available for civilian use, this topic which Dr. Flippin has given us is a very timely one.

There are a couple of questions I would like to ask Dr. Flippin. One is: does it alkalize the urine very strongly and would he comment a little more on the streptomycin in the treatment of syphilis? Again I want to thank Dr. Flippin for coming down here; I think he has given us a most timely topic.

DR. JOHN W. HOWARD (Wilmington): Again I thank Dr. Flippin for coming down. My few remarks are from a laboratory point of view. We are dealing with a drug that is expensive. It is still experimental, and we should tread our way very cautiously both from the point of view of our results and the cost to the patient. Most of the hospitals in Wilmington at the present are set up to do a simple procedure for streptomycin sensitivity. We are not doing a titration. We are doing nothing more than a contact zone, streptomycin impregnated on filter paper, and we get a clearing zone around the test area in which the organism is separated.

I can add my belief to that of Dr. Flippin's that we should be sure before we embark upon a program of streptomycin therapy today.

DR. FLIPPIN: Thus far, we have had no experience with the treatment of syphilis with streptomycin. From preliminary studies elsewhere, there is reason to believe that it is effective. Although I am not certain, I believe that streptomycin is more effective in an alkaline urine. Again, I wish to thank you for this opportunity.

'MODERATE DRINKING' IMPLIES TAKING TWO COCKTAILS A DAY

A moderate drinker takes two cocktails or highballs a day, states a medical consultant in answer to a query in the July 12 issue of *The Journal of the American Medical Association.*

His reply says that "for the average, so-called healthy adult, on a good diet, two cocktails or highballs a day would by most informed people be considered 'taking alcohol in moderation,' particularly if not taken on an empty stomach before the morning breakfast, and if taken shortly before, during or shortly after the evening meal. But taken under identical conditions and rate, this quantity of alcohol would produce much higher blood alcohol in a person weighing 100 pounds than in a person weighing 200 pounds. The late Dr. Raymond Pearl of Johns Hopkins Medical School reported that moderate drinkers live as long as do total abstainers. On the other hand, heavy or so-called excessive drinkers shorten their life span, evidently through the action of alcohol. As regards the immediate and temporary action of alcohol (the degree of inebrity) there are considerable individual variations in tolerance. But it is not yet known whether persons having low tolerance suffer chronic injury more readily. All that can be said at present is that to the average normal adult possible chronic injuries from the amounts of alcohol mentioned have not yet been proved or clearly separated from hereditary factors in the organ potentials, from the inevitable effects of disease, from accidents, from the strain of living and from the aging processes."

Another *Journal* consultant, reviewing the effects of the moderate use of alcohol, states: "One of the best sources of data concerning the effects of the moderate use of alcohol is that offered by the statistical studies made in the Medico-Actuarial Mortality Investigation carried out by a Joint Committee of the Actuarial Society of America and the Association of Life Insurance Directors. The pub-

lished reports in 1914 and again in 1929 consisted in a study of over 2,000,000 policies. In this investigation the term 'moderate drinker' was applied to persons who took an average of two glasses of beer or one glass of whisky or their equivalent daily. Of this group the better class of risks, those who were accepted at the standard rates of premium, indicated a mortality of 15 per cent higher than the average of all insured lives treated as standard risks, i. e. a relative mortality of 115 per cent. It is pointed out, however, that, while the habits were recorded at the time of application, the higher mortality than usual may be due largely to a proportion of the applicants becoming immoderate drinkers at a later date. The death rate in this group was higher than the normal from cirrhosis of the liver, cerebral hemorrhage and pneumonia.

"By comparison, whereas some members of the 'moderate drinker' group were allowed policies at the normal rates of premium, another group, which consisted of those who drank to excess not oftener than three times a year but those whose bouts lasted two or three days at a time, were considered as distinctly hazardous risks, with a relative mortality of 331 per cent."

Does It Pay to Work Harder?

WILLFORD I. KING, Ph. D.,*
New York, N. Y.

Does it pay to work harder? That this question inevitably thrusts itself before every financially successful business and professional man today is clearly indicated by the accompanying table. It reveals how, as income is added, Federal taxes climb, and how the fraction of the added receipts retained by the individual dwindles as income expands.

For the man who earns $4,000 above his exemption, it manifestly pays to work harder and earn $2,000 more, for Uncle Sam lets him keep three dollars out of every additional four that he gains by his hustling. The man making $8,000 above his exemption will probably feel it worth while to add $2,000 to his income, for he is still privileged to keep two out of every three added dollars. However, for the man having an income of $15,000 above his exemptions, the worthwhileness of striving to take in another $5,000 raises serious questions in his mind, for, in his case, the Federal Government takes more than half of the added gains. One can hardly expect the man receiving $100,000 to be much interested in doubling his income, for, if he does, he can only keep for his own use one dollar out of every additional seven.

Obviously, the present income tax law constitutes an effective device for preventing the most efficient business and professional men from fully utilizing their talents. The law acts, therefore, as a damper on production, and hence lowers the income of the average citizen.

In addition, it prevents him from accumulating capital, and thus hampers not only *his* progress, but that of the nation as a whole. These are the results which advocates of progressive taxation persistently refuse to consider. There are none so blind as those who will not see!

HOW ADDED EARNINGS ARE SHARED IN 1947

Individual's Net Income After Exemptions	Additional Income Gained By Working Harder to Reach Next Higher Figure In Left Hand Column	Additional Dollars Taken By Federal Income Tax	Dollars of Gain Remaining After The Tax Is Paid	Per Cent of Gain Remaining After Tax Is Paid
$4,000	$2,000	$494	$1,506	75.2
6,000	2,000	570	1,430	71.5
8,000	2,000	640	1,360	68.0
10,000	5,000	1,992	3,008	60.2
15,000	5,000	2,403	2,597	51.9
20,000	10,000	5,662	4,338	43.4
30,000	10,000	6,194	3,806	38.1
40,000	10,000	6,726	3,274	32.7
50,000	25,000	18,383	6,617	26.5
75,000	25,000	20,092	4,908	19.6
100,000	100,000	85,025	14,975	15.0
200,000	300,000	259,350	40,650	13.6
500,000				

The x-ray film, particularly in surveys, is only a screen in tuberculosis case finding. It can only pick out the normal from the abnormal. It is the important clinical follow-up investigation that must tag the positive carrier. —Maurice Kovnat, M. D., J.A.M.A., Mar. 29, 1947.

Many a maternity patient has received obstetric care in its most literal sensethat is, care which is focused only on her reproductive organs—and died from tuberculosis or diabetes or cancer soon after delivery. Hazel Corbin, R. N., *Jour. of Nursing,* Aug., 1946.

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+ Editorial +

DELAWARE STATE MEDICAL JOURNAL

Owned and published by the Medical Society of Delaware, a scientific society, non-profit corporation. Issued about the twentieth of each month under the supervision of the Committee on Publication.

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Articles are accepted for publication on condition that they are contributed solely to this JOURNAL. Manuscripts must be typewritten, double spaced, with wide margins, and the original copy submitted. Photographs and drawing for illustrations must be carefully marked and show clearly what is intended.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, published by the American Medical Association, Chicago.

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Subscription price: $2.00 per annum, in advance. Single copies, 20 cents. Foreign countries: $2.50 per annum.

VOL. 19 JULY, 1947 No. 7

DECAY OF THE FAMILY

It is alleged that the institution of the family in Western civilization is going on the rocks. *Life* magazine[1] discusses the question editorially, pointing out that according to Dr. Carl Zimmerman, Harvard sociologist, "the Western family has collapsed twice before, in Greece about 300 B. C. and in Rome about 300 A. D., in each case marking the decline of those states." Decay of the family in Greece and Rome was marked by corruption, vanishing birthrate, demigration of parents, juvenile and adult delinquency, says *Life*.

Certainly, accumulating statistical evidence seems to lend weight to the warnings from many sources that something is happening to the modern family. Such a state of affairs should be of the gravest concern to doctors of medicine. It is probably inevitable that as civilizations evolve from their simpler, more rudimentary forms to their complex maturity the diseases of industrial middle age and early atomic-age senescence invade their cells destructively. Oswald Spengler elaborated the thesis in his *Decline of the West* some time ago.

If the family decays, what then becomes of the family doctor? The ready answer would be that he becomes the decayed-family doctor. How near to that status is he now? If the decay of the family is marked by the symptoms recited in our first paragraph, should not medical educators, medical societies, and others interested in the future of medicine, give thought to the fact that a falling birthrate will necessitate fewer obstetricians and pediatricians, but probably more gynecologists, genitourinary practitioners, and psychiatrists. The decayed-family practitioner could conceivably be a combination in one person of formerly separate specialists best calculated to make of him a decayed-family friend and counselor. His premedical curriculum could include law, sociology, the rudiments of police work, philosophy with special emphasis on Spencer and Spengler, abnormal psychology, the rudiments of statism, with possibly some attention to English composition.

The medical curriculum could well omit any attention to all but a certain few infectious diseases, substitute nuclear physics and diseases of irradiation, which may be reasonably expected to increase as more and more radioactive gases and other substances are released. There you have the ideal, shortened course to produce the decayed-family practitioner. Medicine should be ever on the alert to be functional in its service to humanity, wherever that may lead, even to the establishment of the qualifications and training of decayed-family doctors, if need be.—Editorial, *N. Y. S. J. M.*, July 15, 1947.

1 March 24, 1947, p. 36.

"GOLDEN DOZEN" DISCOVERIES ADVANCE MEDICAL PROGRESS

A "Golden Dozen" discoveries that are further advancing medical progress in the United States are listed by Doctors Theodore G. Klumpp, president, and Justus B. Rice, vice-president and medical research director of the Winthrop Chemical Company in a review appearing in "Record of Chemical Progress" published by the Kresge-Hooker Scientific Library, Wayne University, Detroit.

Authors of the papers noted that the synthesis of penicillin was a notable achievement of 1946, but stated it was "extremely unlikely that synthetic penicillin will ever be able to compete with the product derived from mould, because of the astronomical quantities of the latter now made possible by mass production.

"The lowering of costs made possible by mass production methods from $20 for a sufficient amount to treat a case of gonorrhea three years ago to only a few cents now puts penicillin within the grasp of every patient," the paper states. "Although cost of streptomycin, another antibiotic, is still high, there has been a corresponding decrease, with further reductions in sight."

Listed as the twelve "golden" medicinal advances of 1946 are: radioactive isotopes, by-products of the atomic pile; two antihistamine drugs, pyribenzamine and benadryl, that "appear effective in controlling symptoms of hay fever and uticaria"; the antibiotic, streptomycin, the value of which was "placed on a firm foundation in 1946"; cytochrome C, an enzyme, useful in such diverse disorders as various kinds of shock, angina pectoris, Raynaud's disease, barbiturate poisoning, pulmonary emphysema, degenerative diseases associated with arteriosclerosis and certain cerebral dysfunctions; rutin, a flavonol compound, derived from green buckwheat, found useful in diabetic retinitis; the metabolic agent, n-propyl thiouracil, that may prove to be "a really effective, safe, medical treatment for many cases of thyrotoxicosis"; dengue fever vaccine; mumps vaccine; the antimalarial aralen; the progress made in synthesis of compounds closely similar to vitamin A; the use of curare, the ancient Indian arrowhead poison, in anesthesia and in the treatment of conditions characterized by muscle spasm or spasticity; and, finally, advances made in cholera therapy, sharply reducing mortality by the use of sulfadiazine and sulfaguanadine.

Detailed comment follows:

1—*Radioactive isotopes*: Invention of the atomic pile came at precisely the right moment in medical history. By-products of the atomic pile may yet pay the debt to humanity contracted at Hiroshima and Nagasaki.

2—*Antihistamine drugs*: Two, pyribenzamine and benadryl, appear to be the most effective in controlling the symptoms of hay fever and uticaria. They have been particularly useful in preventing or ameliorating the severity of uticaria produced by penicillin in sensitive individuals. Pyribenzamine appears to have a slight edge on benadryl.

3—*Antibiotics*: During 1946, the value of streptomycin was placed on a firm foundation. Perhaps its most dramatic effects are seen in the treatment of tularemia. Hardly less dramatic are its effects on certain forms of meningitis, bacteremia and urinary tract infections untouched by penicillin, that is, those caused by susceptible strains of Pfeiffers bacillus B. Coli, B. proteus, Friedlander's bacillus, B. pyocyaneus, and Salmonella. In cases of peritonitis, endocarditis, and chronic lung infections produced by these organisms and some other susceptible species, its activity is definite, but the results of treatment are usually less spectacular. Insufficient evidence is available at present to assess with any degree of certainty the value of streptomycin in typhoid fever and brucellosis. While streptomycin cannot be relied upon to cure tuberculosis, it does, nevertheless, exercise a profoundly beneficial effect on the course of the disease.

4—*Enzymes*: One of the most intriguing preparations placed in clinical research in 1946 is cytochrome C, an "enzyme," which plays an important role in controlling tissue oxygeneration. It appears at the present time to be useful in such diverse disorders as various kinds of shock, angina pectoris, Raynaud's disease, barbiturate poisoning, pulmonary emphysema, degenerative diseases associated with arteriosclerosis and certain cerebral dysfunctions. Possible effects on the aging process invite the imagination.

5—*Flavonol compounds*: Rutin, a flavonol compound similar chemically to hesperidin, but derived from green buckwheat, has been found useful in diabetic retinitis.

6—*Metabolic agents*: In n-propyl thiouracil, a derivative of thiouracil, there are excellent grounds for optimism. It may prove to be the "bee without the sting" and that a really effective, safe, medical treatment for many cases of thyrotoxicosis has been found.

7—*Dengue fever vaccine*: Extensive clinical trials proved the worth of Sabin and Schlesinger's vaccine for dengue fever. For the first time good protection is possible against this "heart and back-breaking" disease.

8—*Mumps Vaccine*: A formal-inactivated suspension of mumps virus was found to give some degree of protection to children. Although the present vaccine is not the final word in mumps prophylaxis, it does appear to be the first successful step toward that goal.

9—*Antimalarials*: During 1946 the powerful new antimalarial, aralen, reached the market and came into widespread use. Although its toxicity makes it unlikely that pentaquine, another new antimalarial, will be widely used, the discovery of its point of action demonstrates the exoerythocytic cycle of the malarial parasite, causing relapses, is vulnerable to attack. A true causal prophylactic for malaria and a permanent cure for all types of the disease are in sight.

10—*Vitamins*: Notable progress has been made with the synthesis of compounds closely similar to vitamin A. None yet produced, however, approach crystalline vitamin A in biologic potency.

11—*Curare*: When curare is used together with an anesthetic agent for major surgical procedures, perfect muscular relaxation can be obtained with very much smaller amounts of anesthetic than would otherwise be required. The dose must be carefully controlled and expertly gauged to prevent paralysis of respiration. In addition to its use in anesthesia, it is finding a place in the treatment of conditions characterized by muscle spasm or spasticity.

12—*Cholera therapy*: During 1946 chemotherapy has been extended to one of the most ancient and deadly of epidemic diseases, cholera. In previous epidemics, cholera has carried a mortality up to 70 per cent, but in a recent study the mortality has been sharply reduced by the use of sulfadiazine and sulfaguanadine. Only three deaths occurred among 19 seriously ill patients whereas 23 of 24 untreated succumbed. The value of rehydration was strikingly demonstrated. In a group of 35 patients treated with blood plasma and chemotherapy, there was no mortality.

Cancer of the Cervix

Married women who bear children are more susceptible to cancer of the cervix than unmarried women, according to a 21-year study of 1,342 patients who were treated at Bellevue Hospital, New York, one of the largest general hospitals in the country.

Writing in the June issue of the *American Journal of Roentgenology and Radium Therapy*, published for medical specialists in x-ray and radium, two New York physicians connected with Bellevue Hospital state that child bearing appears to be an important factor in the high incidence of cervical cancer, which is one of the commonest of cancers occurring in women.

The doctors who made their report in the JOURNAL were Ira I. Kaplan, Director of the Radiation Therapy Department, and Rieva Rosh, visiting Radiation Therapist, of Bellevue Hospital, which is a free city institution.

They reported on the results of x-ray and radium treatment on 1,342 patients, with cancer of the cervix over a 21-year period. Of the 1,342 patients, 426 were "so extensively involved" that no active treatment could be attempted.

Of the 916 patients who underwent treatment, 853 were married and 13 single. In 50 cases the marital status was not recorded. Of the known married patients, 777 had borne one or more children, and of these 418 bore four or more children.

"It appears therefore," the doctors wrote, "that bearing children did have a definite influence on the formation of cancer in these cases."

The two doctors said that most of the cervical cancer cases seen at Bellevue are in the advanced stages.

"New York City has a very large Negro population and one would expect a large num-

ber of cases of cervical cancer in Negro women," the doctors stated in their report. "However, only 163 were of this race in our service. There were 707 white patients treated and in 46 cases color was not recorded.

"While as a whole the number of Jewish patients coming to Bellevue Hospital is still small, our survey shows that cervical cancer is not common among Jewish women. Of the 1,342 cases, only 25 were in Jewish women. The reason for this small number is not definitely understood."

The two New York physicians stated that on the basis of their experience over 21 years, they believe that x-ray and radium are the best combination for treatment of cervix cancer. X-ray threapy, they said, should precede the local application of radium, because it is "extremely effective in controlling pelvic involvement, alleviates infection and often appreciably reduces the local lesion."

Medical Publications Needed Overseas

As a result of war and persecution, doctors, dentists and technicians in allied fields throughout Europe have been deprived for more than ten years of news and latest developments in their professions—the kind of news and analysis contained in this Journal.

When you have finished this issue, put it to work by sending it to the SOS (Supplies for Overseas Survivors) Collection of the Joint Distribution Committee, 1539 Troy Avenue, Vanderveer Park, Brooklyn, N. Y. It will be placed in a library in a D. P. camp, child care center, hospital or school, for use by professionals desperately anxious to bring themselves up-to-date on the knowledge forcibly kept from them by the Nazis.

Probably no greater mental trauma is ever inflicted by a physician than when he first tells a patient that he or she has tuberculosis. The patient probably knows absolutely nothing about tuberculosis except that it is a dread disease. Material and social problems combined with the psychological problems of separation from family, complete change of living routine, sudden cessation of all activity, ignorance of the disease and what it will mean to him and an unknown future is apt to create in the patient a mental turmoil which is a known detriment to his eventual recovery and return to a useful life. C. J. Stringer, M. D., Hospitals, August, 1946.

During the past 50 years tuberculosis has been declining more rapidly in childhood and adolescence than at any other age. In fact, tuberculosis has become primarily a disease of middle-aged and old people. In Massachusetts the reaction rate to the tuberculin test in school children dropped 50 per cent between 1925 and 1940, and the amount of pulmonary tuberculosis found by mass examination fell proportionately. In Tennessee, with a high tuberculosis death rate, the state department of health reports five cases per 1,000 among high school students, compared with two per 1,000 found in Massachusetts. Alton S. Pope, M. D., NTA Bull., Nov., 1946.

BOOK REVIEWS

Clinical Allergy: A Monograph on the Management and Treatment of Allergic Diseases, for General Practitioners and Students of Allergy. By Alexander Sterling, M. D., and Bea Sterling Hollander, A. B., M. D. Pp. 198. With 16 illustrations. Cloth. Price, $5.00. International Universities Press, New York, 1947.

This small volume is essentially a primer on clinical allergy. The subject is briefly discussed and expounded largely by the case presentation method.

A book of this type would little interest a physician frequently meeting cases of allergy in his practice. For the individual who occasionally sees or more frequently refers his cases, this volume may serve as his catechism, if he desires to improve his knowledge.

Physician's Handbook. By John Warkentin, Ph. D., M. D., and Jack D. Lange, M. D. Fourth Edition. Pp. 282. Price, $1.50. University Medical Publishers, Chicago, 1947.

This conveniently sized pocket manual is remarkable in the wealth of information it gives in the compass of its pages. It is admirably suited for the intern and younger physician, as well as for the older practitioner. A quick perusal of its pages will refresh the memory on many a clinical or laboratory detail of value.